REMARKS

Claims 38-85 are pending in the application and have been examined. Claims 38-85 stand rejected. Claim 69 has been amended. Entry of the amendments to Claim 69, and reconsideration and allowance of Claims 38-85 is respectfully requested.

Interview Summary

Applicants' attorney thanks the Examiner for granting an interview on January 30, 2007. The participants in the interview were Examiner John Brusca and applicants' attorney Tineka J. Quinton.

During the interview a proposed amendment to Claim 69 was discussed and the Examiner stated that it would likely be entered. The Examiner indicated that if the proposed amendment to Claim 69 were to be entered, it would overcome the rejection of Claim 69 under 35 U.S.C. § 101. The rejection of record under 35 U.S.C. § 103(a) was also discussed without agreement.

The Rejection of Claim 69 Under 35 U.S.C. § 101

Claim 69 has been amended as suggested by the Examiner to include "one or more sequences of instructions, which, when executed by one or more processors, causes the processors to perform a comparison function for comparing output signal data from a probe matrix with the data stored in the output structure database of step (a)." Support for this amendment is found throughout the specification as filed, for example at page 7, lines 3-30; FIGURE 1; and FIGURE 4. It is submitted that Claim 69, as amended, is directed to functional descriptive material and therefore complies with the statutory requirement of 35 U.S.C. § 101. Entry of the amendment and removal of this ground of rejection is respectfully requested.

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The Rejection of Claims 38-53, 55-66, 68-83, and 85 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Gress et al., in View of Granelli-Piperno et al. in View of Either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991

Claims 38-53, 55-66, 68-83, and 85 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al., in view of either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991. The Examiner has taken the view that Gress et al. discloses a method of assaying patterns of transcription by use of labeled cDNA from mouse and human cells by the use of a cDNA X-Y coordinate grid array of probes. Gress et al. is further cited as disclosing the importation of resulting data via an electrical signal of a Phosphorimager to a computer implemented relational database. The Examiner acknowledges that Gress et al. does not show (1) subjection of assayed cells to different stimuli; (2) comparison of the transcriptional profile of cells that have received different stimuli; (3) assay of discrete portions of the complete number of genes of the cell; or (4) use of probes with a predetermined sequence of nucleotides. The Examiner then cites Granelli-Piperno et al. as disclosing that assay of expression of genes after treatment of cells with drugs allows a determination of the effect of the drug on individual gene expression via intensity of a film image on an autoradiograph. Fodor et al. '91 or '98 is cited by the Examiner as disclosing a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. The Examiner then concludes that it would have been obvious to a person of ordinary skill to modify the method of Gress et al. by assaying cells that have received treatments with different drugs according to the method of Granelli-Piperno et al. because Granelli-Piperno et al. shows that such an analysis serves to gain insights on the mechanism of action of the drug. The Examiner takes the view that it would have been further obvious to assay additional numbers of genes as desired to determine the effect of a drug on additional genes. The Examiner further concludes it would have been obvious to make and use an array of probes with a predetermined sequence as disclosed by

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Fodor et al. '91 or '98. Applicants disagree with the Examiner's conclusions for the following reasons.

It is submitted that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the referenced teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); Manual of Patent Examining Procedure (M.P.E.P.) (8th ed., August 2001, rev. May 2004) Sections 706.02(j), 2142 and 2143. As stated in *In re Fritch*, 972 F.2d 1260, 1266, 23 U.S.P.Q.2d 1780, 1784, (Fed. Cir. 1992), it is impermissible to use the claimed invention as an instruction manual or "template" in attempting to piece together isolated disclosures of the prior art so that the claimed invention is rendered obvious.

Moreover, Section 103 specifically requires consideration of the claimed invention as a whole. As pointed out recently by the Federal Circuit, "[i]nventions typically are new combinations of existing principles or features . . . the 'as a whole' instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might break an invention into its component parts (A+B+C), then find a prior art reference containing A, another containing B, and another containing C, and on that basis alone declare the invention obvious. Section 103 precludes this hindsight discounting of the value of new combinations by requiring assessment of the invention as a whole." *Ruiz v. A.B. Chance Company*, 357 F.3d 1270, 69 U.S.P.Q.2d 1686, 1690 (Fed. Cir. 2004).

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It is submitted that the Gress et al. reference fails to teach or suggest numerous elements of the claimed invention, and even if the teachings of Gress et al. were to be combined with the references cited by the Examiner, which there is no motivation to do, the combination would not result in the invention as claimed. The Examiner has acknowledged that Gress et al. does not show (1) subjection of assayed cells to different stimuli; (2) comparison of the transcriptional profile of cells that have received different stimuli; (3) assay of discrete portions of the complete number of genes of the cell; or (4) use of probes with a predetermined sequence of nucleotides. In addition, applicants wish to point out that Gress et al. also fails to teach or suggest (5) quantitative measurement of relative levels of gene expression; (6) comparison of a transcriptional profile within a species; or (7) storing in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus; and (ii) with the identity of the identified gene.

In fact, it is submitted that Gress et al. actually teaches away from the claimed invention for at least the reasons described in the Response to Office Action, mailed on June 7, 2006, incorporated herein by reference. Briefly summarized, applicants previously pointed out that the methods of Gress et al. were used to identify clones in a cDNA library containing mRNA sequences expressed at least at a middle to high abundance level, with the necessity of extensive controls due to the high level of background hybridization observed from polyA tails and repeated sequences. In response to applicants' previous arguments however, the Examiner has maintained the position that Gress et al. shows that despite the necessity of controls, it is possible to quantify levels of gene expression by their method, with particular reference to Figure 2 and Table 1. Applicants disagree with the Examiner's interpretation of Gress et al. for the following reasons.

Applicants note that Table 1 does not describe a comparison of gene expression levels, but rather presents results showing the total number of uncharacterized cDNA clones on a

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nitrocellulose filter that hybridized to a panel of cDNA pools obtained from various tissues of various organisms. In fact, the results of Table 1 demonstrate that the Gress et al. method is not suitable for same-species analysis due to the high background hybridization resulting from repetitive sequences. The authors in Gress et al. acknowledge this drawback of the method, stating with regard to Table 1 "cDNA pool probes were preferentially prepared from a different species (*e.g.*, mouse) than the cDNA library (human) to reduce unspecific hybridization due to human-specific repetitive sequences (*e.g.* Alu)." See Gress et al., page 616, 1st Col., and page 612, 1st Col. Therefore, it is submitted that Gress et al. teaches away from comparing transcript levels of a panel of genes from stimulated and unstimulated cells derived from a subject, as claimed.

Moreover, it is apparent from the results in Table 1 that the nitrocellulose filters containing the cDNA pools described in Gress et al. contain numerous uncharacterized repetitive sequences and non-coding sequences that do not specifically hybridize to a transcript of an expressed gene. In this regard, Gress et al. states with reference to Table 1 "[a] large number of these positives could not be used for further analysis as they hybridized with one of the control probes as well (up to 45% for HFB and up to 16% for Drosophila)." Gress et al., page 612, 2nd Col. As further described "[o]n average, one clone in a pool hybridized to 10-14 clones on each HFB library filter (Fig 5a and b)." Gress et al. at page 613, 2nd Col. In contrast, the present invention is directed to the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a predetermined sequence *hybridizable with a different identified gene*, transcript or cDNA derived from the gene of a living thing.

The Examiner has cited Figure 2 of Gress et al. as disclosing the ability to quantify levels of gene expression. Applicants also disagree with the Examiner's conclusion in this regard. Figure 2 merely shows the identification of positive versus negative clones, where positive clones were identified as having a level of expression detected over a chosen threshold value. As

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stated by the authors in Gress et al., Figure 2 shows "typical grey value patterns as produced by different cDNA pool and control hybridizations for a subset of HFB library clones." Gress et al., legend to Figure 2, page 614. All the grey values shown in Figure 2 representing various clones on the hybridization filter are expressed with a value represented as either "1X" (*e.g.* positive) or "zero" (*e.g.* negative) on a scale from zero to 2X. As further described in Gress et al., "[a] large scale of grey values is generated in one single-tissue cDNA pool hybridization, and the determination of adequate grey value thresholds *allowing one to distinguish between 'positives and negatives' in each individual experiment* is not a simple matter." See Gress et al. at page 616, 2nd Col.

Moreover, it is clear that the purpose of the approach described in Gress et al. is to identify previously uncharacterized mRNAs for further analysis, which teaches away from the use of predetermined sequences as claimed. For example, Gress et al. explicitly states "[t]he approach presented here will be of special value in *selecting clones for the generation of expressed sequence tagged sites (ESTs)* for mapping and sequencing the human genome." See Gress et al. at page 617, 2nd Col. Therefore, the Examiner's proposed modification of Gress et al. to include predetermined sequences would conflict with the intended purpose stated by Gress et al., because a hybridization filter having predetermined sequences would not allow for the identification of new, previously uncharacterized mRNAs, as described in more detail below.

Accordingly, it is respectfully submitted that the teachings of Gress et al. fail to teach or suggest numerous elements of the claimed invention, and moreover, when taken as a whole, Gress et al. teaches away from the method as claimed, and provides no expectation of success for comparing transcript levels from stimulated and unstimulated cells from a subject.

It is submitted that the shortfalls of the Gress et al. reference are not cured by the teachings of Granelli-Piperno et al. and/or Fodor et al. '98 or '91, either alone or in any

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combination. Granelli-Piperno et al. describes Northern blot analysis of nine lymphokine mRNAs known to be involved in T cell stimulation in order to compare expression of the lymphokine mRNA expression in terms of kinetics, mitogen requirements and sensitivity to cyclosporin A. It is noted that Granelli-Piperno et al. fails to teach or suggest at least the use of a matrix comprising a plurality of units wherein each unit confines a probe comprising a predetermined sequence hybridizable with a different identified gene, transcript or cDNA derived from the gene of a living thing, or storing in digital form an electric output signal in an output signal data structure, wherein each stored digital signal is associated (i) with a stimulus; and (ii) with the identity of the identified gene. Rather, the methods described in Granelli-Piperno et al. relate to the use of a nitrocellulose filter containing total cellular RNA isolated from T cells that is hybridized with individual probes specific to nine genes known to be involved in T cell stimulation (see Granelli-Piperno et al., page 923, third paragraph). Moreover, as described above, there is no motivation to modify the method of Gress et al. with the teachings of Granelli-Piperno et al. because Gress et al. teaches away from the claimed invention. For example, one would not be motivated to compare stimulated and unstimulated cells from the same subject using the methods of Gress et al. due to the high background resulting from the numerous uncharacterized repetitive sequences, and due to the inability to quantitatively measure relative levels of gene expression. Therefore, one of skill would not have a reasonable expectation of success. Finally, even if one were to improperly combine the teachings of Gress et al. and Granelli-Piperno et al., the references fail to disclose all the elements of the claimed invention.

With regard to Claim 49, the Examiner has taken the view that it would have been obvious to assay additional numbers of genes as desired to determine the effect of a drug on additional genes. Applicants disagree. Claim 49 depends from Claim 38 and is believed to be allowable for at least the reasons stated herein in connection with Claim 38. Moreover, Claim 49

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is further distinguished from the cited references because it contains an additional limitation that "the probe matrix comprises probes having sequences that are hybridizable with at least 0.5% of the of the genes of said living thing." The proposed motivation by the Examiner to modify the referenced teachings to assay additional numbers of genes does not derive from the references themselves. It is noted that there is no teaching or suggestion in Granelli-Piperno et al., or in any other reference cited by the Examiner, to detect physical signals from a plurality of units ordered in a probe matrix, wherein each unit confines a probe comprising a pre-determined sequence that is hybridizable to at least 0.5% of the genes of the living thing, in order to analyze the effects of subjecting a living thing to a stimulus as claimed. As described above, Granelli-Piperno et al. describes a directed study to monitor the effect of cyclosporin on a set of nine lymphokine genes. As described in Granelli-Piperno et al., cyclosporin A was already known to effect the expression of lymphokine mRNAs known to be involved in T cell stimulation (see Granelli-Piperno et al., page 922). Absent some suggestion to assay a wider array of genes, such as at least 0.5% of the genes of a living thing, to measure the effect of a stimulus on a living subject, there is no motivation or expectation of success to attempt to modify the method of Gress et al. with the teachings of Granelli-Piperno et al.

The Examiner cites Fodor et al. '91 or Fodor et al. '98 as teaching a method of synthesizing a dinucleotide of a predetermined sequence by a photolithographic process. The Examiner further takes the view that a modification of the array as proposed by the Examiner by use of predetermined sequences of probes shown in Fodor et al. '91 does not conflict with the purpose of Gress et al. of using the array for *identification* of highly expressed cDNA clones. Applicants respectfully disagree with the Examiner's conclusion in this regard. As described above, Gress et al. explicitly states that the approach is of value in *selecting clones for the generation of expressed sequence tagged sites* for mapping and sequencing the human genome. It is clear in Gress et al. that the objective is to identify previously uncharacterized clones that are

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expressed for *future* sequencing and analysis. Therefore, the Examiner's proposed modification of Gress et al. to include the use of predetermined sequences would conflict with the stated purpose in Gress et al. of identifying and sequencing new, previously uncharacterized mRNA transcripts.

Accordingly, it is respectfully submitted that the combination of Gress et al. with Granelli-Piperno et al. and Fodor et al. '91 or '98 fails to teach, suggest, provide motivation to make, or otherwise render obvious the invention as claimed in independent Claims 38, 56, and 70. Moreover, even if combined, which there is no motivation to do, none of the cited references teaches or suggests all the claim limitations. Removal of this ground of rejection is respectfully requested.

The Rejection of Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Gress et al., in View of Granelli-Piperno et al. in View of Either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991, and Further in View of Watson et al.

Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gress et al., in view of Granelli-Piperno et al., in view of either Fodor et al. 1998 (U.S. Patent No. 5,800,992) or Fodor et al. 1991, and further in view of Watson et al.

The Examiner characterizes the rejected claims as being drawn to assays utilizing fungal cells and cites Watson et al., pages 573-575, for its teaching that these cells contain genes that are regulated by stimuli such as metabolites.

For at least the reasons set forth in connection with the rejection of Claims 38-53, 55-66, 68-83, and 85 under 35 U.S.C. § 103(a), it is submitted that it is not obvious to combine the teachings of Gress et al., Granelli-Piperno et al., or Fodor et al., as suggested by the Examiner. This deficiency is not cured by the teachings of Watson et al. Applicants respectfully request

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that the rejection of Claims 38, 49-51, 54, 56, 63-65, 67, 70, 80-82, and 84 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, the application is believed to be in condition for allowance. If any issues remain that can be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone the applicants' attorney at 206.695.1655.

Respectfully submitted,

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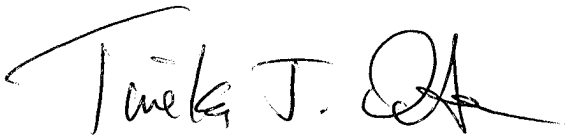

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